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PATENT & TRADEMARK OFFICE

I hereby certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Hon. Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 on this 12th day of February 2004.

By Kelley D. Surprenant
(Signature of person mailing)
Kelley D. Surprenant
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:
Kaneko et al.

APPLICATION NO.: 09/892,081

FILING DATE: 26 June 2001

TITLE: Novel Macrolide Antibiotics

Examiner: E. Peselev

Group Art Unit: 1623

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

37 CFR § 1.131 DECLARATION OF TAKUSHI KANEKO

Sir:

1. I, Takushi Kaneko, Ph.D., am the first-named inventor of the captioned application.

2. I completed the presently claimed invention before 11 May 2000.

3. Exhibit A hereto is a copy of a note and invention disclosure (seven pages total) that I prepared and delivered to Seth Jacobs, a Pfizer patent attorney, before 11 May 2000. Exhibit A is redacted only as to the date of the note and invention disclosure, which is before 11 May 2000.

4. Exhibit A describes compounds of the presently claimed invention and their preparation. More specifically, there are disclosed therein a generic formula, a synthetic scheme, and an example, of the present invention.

5. I further declare that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United

States Code, and that such willful false statements may jeopardize the validity of the above-captioned application or any patent issuing therefrom.

February 3rd, 200X
Date

Takushi Kaneko
Takushi Kaneko, Ph.D.

[redacted]

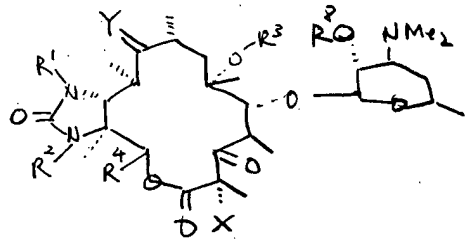
Seth,

Since I will be away next week and don't have time to type this, I am sending you a hand written version.

I feel this should be sufficient to get the process moving.

If you have any questions, just send me an email please.

Scope of the Claim.



R^1, R^2, R^3 = independently H, lower alkyl, ar(lower)alkyl, heteroarylalkyl

Y = O, $NHOR^5$, H + NHR^6

R^5 = lower alkyl, aryl, ar(lower)alkyl

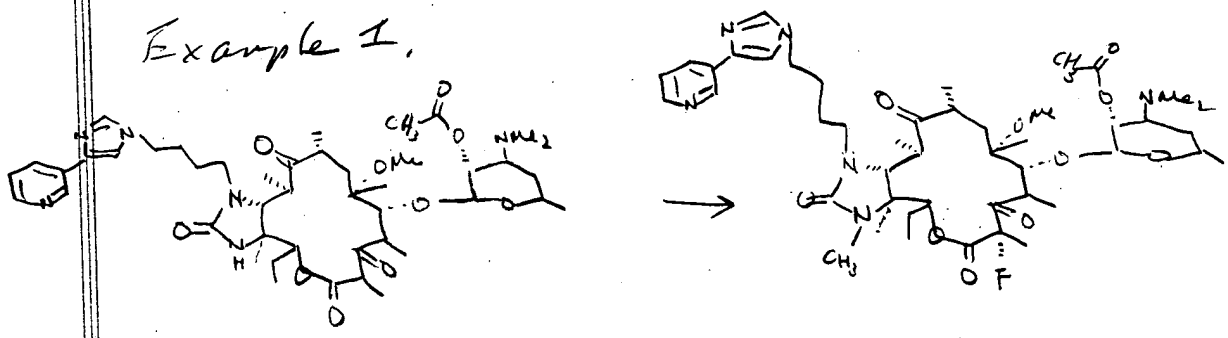
R^6 = " , " , "

X = halogen.

R^4 = H, C_1-C_{10} alkyl, C_2-C_8 alkenyl, C_2-C_4 alk
C_6-C_{12} aralkyl. (a la Biotica patents)

R^9 = H, or C(O) C_1-C_6 alkyl, benzyl, benzyloxycarbonyl $(C_1$-C_6 alkyl$)_3$silyl

Example 1.

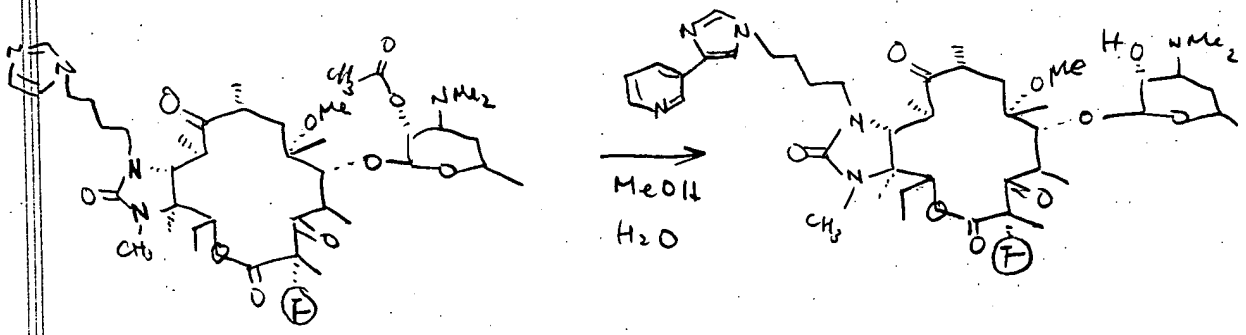


1 → 2

To a solution of 1 (18 mg, 0.021 mmol) in 1.5 mL of DMF was added at −78 °C a solution of KHMDS (42 µL of 0.5 M solution in toluene, 0.021 mmol). After 15 min of stirring at −78 °C, a solution of Selectfluor (8.2 mg, 0.023 mmol) in 500 µL of DMF was added dropwise. After 10 min of stirring at −78 °C, Methyl iodide (15 µL 0.062 mmol) was added dropwise after 15 min. The solution was stirred at this temperature for 11 min. The reaction was quenched by addition of a saturated $NaHCO_3$ solution and ethyl acetate. The organic layer was washed with a saturated $NaHCO_3$ solution and brine. Drying over Na_2SO_4 and removal of the solvent gave 18 mg of crude product. It was chromatographed on silica gel (10 % CH_3OH – CH_2Cl_2) to give 12 mg (64 %) of the title compound; MS 885 (M+1).

esh KHMS
:0 µL, 0.025 mmol)
as added.

Example 1 (continued)

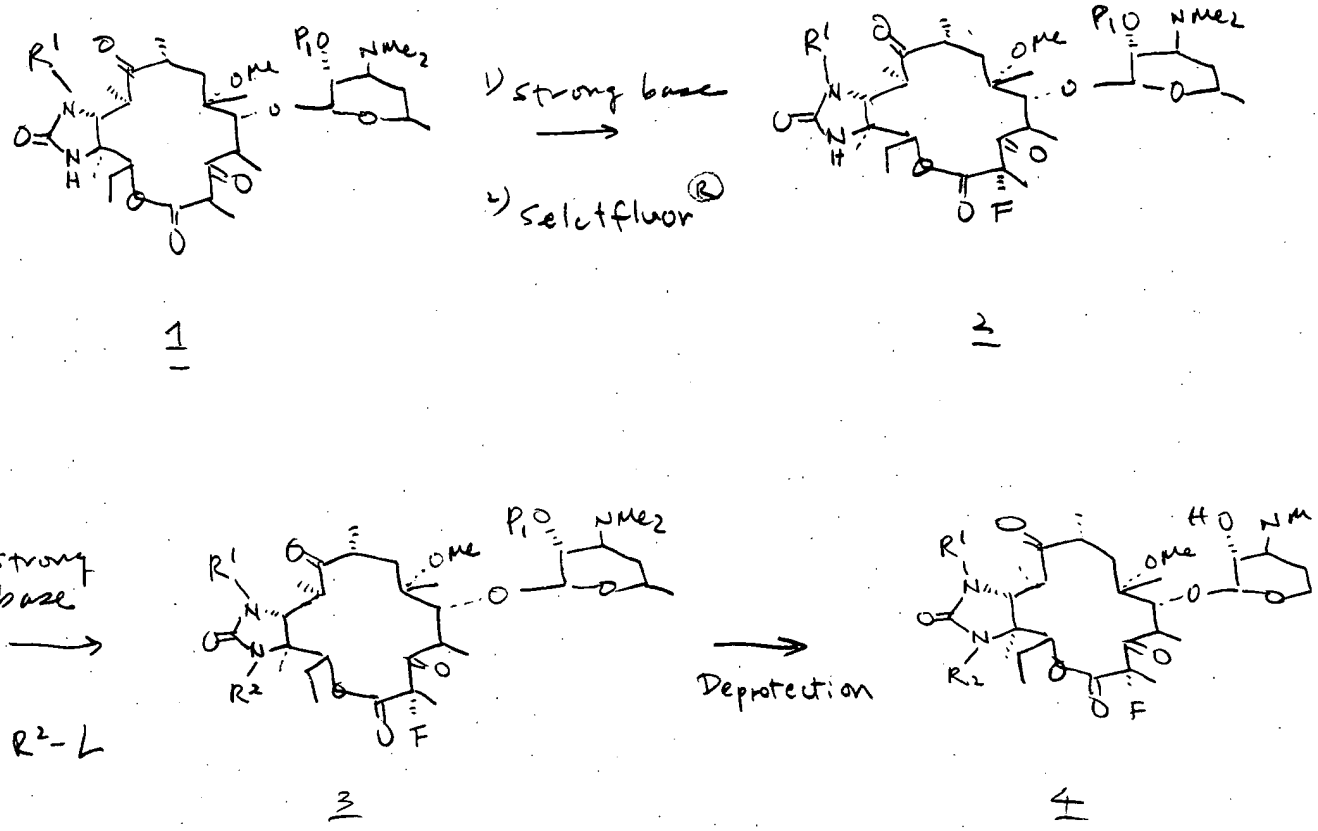


2 3

Compound 2 was dissolved in 1 mL of MeOH and 2 drops of water was added. The solution was stirred overnight at room temperature. Evaporation of the solvent gave 12 mg of the title compound; MS 842 (M+1).

Synthetic Schemes

Scheme I.



Explanation of Scheme I.

Cyclic urea 1 can be prepared according to our previous application PC-10145.

Compound 1 ($R^1 \neq H$) is then treated with strong base such as potassium hexamethyldisilazide (i.e., KHMDS), lithium diisopropylamide (LDA), or sodium hydride in an inert solvent such as DMF or THF at temperature -78° to 0°C, preferrably -78°C for 5min to 3 hrs, preferrably 15 min.

Then a fluorinating agent such as Selectfluor® or N-fluorosulfonimide

in an inert solvent such as DMF or THF at -78° to 0°C, preferrably -78° for 5 min to 3 hrs, preferrably 15 min.
Then an alkylating agent R^2-L (L is a leaving group such as halogen, mesylate or tosylate). is added and the reaction is stirred for 15 min to 12 hrs, preferrably 30 min at -78° to 50 °C, preferrably at room temperature

The protecting group P' is then removed. In the case of P' = Ac, by stirring in wet methanol at 0° to 50°C, preferrably room temperature, for 0.5 hrs to 20 hrs., preferrably 12 hrs.

In general, fluorination at C2 of macrolide is covered in our application PC 105-11.

The cyclic urea derivatives are covered in our application PC 101451.